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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,865	01/09/2002	Muralidhara Padigaru	21402-237 (CURA-537)	5326

7590 08/10/2004

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Boston, MA 02111

EXAMINER

MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/042,865

Applicant(s)

PADIGARU ET AL.

Examiner

Joseph F Murphy

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 5/24/2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 9-10, 12-41 is/are pending in the application.
- 4a) Of the above claim(s) 1-4, 15-29, 31, 32 and 34-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5, 9-10, 12-14, 30, 33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- 1) ☐ Certified copies of the priority documents have been received.
 - 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
 - 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 05232003 04292002.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: Sequence Comparison A.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of claims 5, 9-10, 12-14, 30, 33, drawn to the polynucleotide encoding the polypeptide of SEQ ID NO: 28 in the response filed 5/24/2004 is acknowledged. Claims 1-4, 15-29, 31-32, 34-41 are withdrawn from consideration pursuant to 37 CFR 1.142(b).

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

Inventorship

In view of the papers filed 5/24/2004, the inventorship in this nonprovisional application has been changed by the deletion of Alsobrook II, John; Boldog, Ferenc L.; Burgess, Catherine E.; Casman, Stacie J.; Edinger, Shlomit Rebecca; Ellerman, Karen E.; Gangolli, Esha A.; Gerlach, Valerie L.; Grosse, William M.; Gunther, Erik; Guo, Xiaojia Sasha; Li, Li ; MacDougall, John R.; Malyankar, Uriel M.; Miller, Charles E.; Millet, Isabelle; Patturajan, Meera; Peyman, John A.; Rothenberg, Mark E.; Shenoy, Suresh G.; Smithson, Glenda', Spytek, Kimberly A.; Stone, David J.; Taylor, Sarah ; Tchemev, Velizar T.; Vemet, Corine', Zerhusen, Bryan D.; and Zhong, Mei.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Claim Rejections - 35 USC §§ 101, 112, first paragraph

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 9-10, 12-14, 30, 33 are rejected under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of this protein or its significance. The claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Novel biological molecules lack well-established utility and must undergo extensive experimentation. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

It is clear from the instant specification that the nucleic acid encoding the NOV13 polypeptide has been assigned a function because of its similarity to known proteins. However, it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors (Doerks et al.1998). These errors can be due to sequence similarity of the query region to a region of the alleged similar protein that is not the active site, as well as homologs that did not have the same catalytic activity because active site residues of the characterized family were not conserved (Doerks et al. page 248, column 3, fourth and fifth

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paragraphs). Inaccurate use of sequence-to-function methods have led to significant function-annotation errors in the sequence databases (Doerks et al. page 250, column 1, third paragraph). Furthermore, Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

After complete characterization, this protein may be found to have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 USPQ 689 (Sup. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

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"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to a nucleic acid encoding a polypeptide which has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as NOV13, the instant invention is incomplete. The polypeptide encoded by the nucleic acids of the instant invention is known to be structurally analogous to proteins that are known in the art as glucuronosyl transferases. In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in the identification of substances which inhibit its activity is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real world" use for NOV13 then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Claims 5, 9-10, 12-14, 30, 33 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial

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asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Even if, arguendo, a patentable utility is found for the nucleic acid encoding SEQ ID NO: 28, claims 9-10, 12-14, 30, 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, which would enabling for a nucleic acid encoding a full-length NOV13 polypeptide of SEQ ID NO: 28, does not reasonably provide enablement for a naturally-occurring allelic variant of a nucleic acid encoding SEQ ID NO: 28, or a nucleic acid encoding a naturally-occurring allelic variant of a polypeptide of SEQ ID NO: 28, or a nucleic acid which hybridizes to a nucleic acid encoding SEQ ID NO: 28, or a nucleic acid which comprises a sequence that differs at no more than 20% of the nucleotides in the coding sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to naturally-occurring allelic variants of a nucleic acid encoding SEQ ID NO: 28, or nucleic acids encoding a naturally-occurring allelic variant of a polypeptide of SEQ ID NO: 28, or nucleic acids which hybridizes to a nucleic acid encoding SEQ ID NO: 28, or nucleic acids which comprises a sequence that differs at no more than 20% of the nucleotides in the coding sequence. The claims are overly broad since insufficient guidance is provided as to which of the myriad of variant encoded polypeptides will retain the characteristics of NOV13. The claims are directed to variant nucleic acids encoding variant polypeptides. However, Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of NOV13. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic

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effects on the protein's function. As an example of the unpredictable effects of mutations on protein function, Mickle et al. (Mickle JE et al. Genotype-phenotype relationships in cystic fibrosis. *Med Clin North Am.* 2000 May;84(3):597-607) teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving rise to the CF phenotype. Thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (Voet et al. *Biochemistry*. 1990. John Wiley & Sons, Inc. pages 126-128 and 228-234) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Additionally, Yan et al. teaches that in certain cases, a change of only two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). Since the claims encompass variant polypeptides and

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given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The claims do not set forth a functional limitation for the encoded variant polypeptides. Additionally, the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides. Since the claims do not enable one of skill in the art to make and use the claimed polypeptides, but only teaches how to screen for the claimed polypeptides, and since detailed information regarding the structural and functional requirements of the polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, since Applicant has only taught how to test for polypeptide variants of NOV13, and has not taught how to make polypeptide variants of NOV13, it would require undue experimentation of one of skill in the art to make and use the claimed nucleic acids.

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Additionally, claims 30-31 would not be enabled insofar as they read on SEQ ID NO:27. First, the breadth of the claims is excessive since the claims read on all pharmaceutical compositions to treat all diseases. Applicants have provided no guidance or working examples of any methods of treatment for any diseases using this protein, including any data or treatment regimen. Furthermore, it is not predictable to one of ordinary skill in the art how to use a pharmaceutical composition. Applicants can overcome this rejection by amending the claims to recite the proteins which are "in a pharmaceutically acceptable carrier."

Claims 9-10, 12-14, 30, 33 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to The claims are drawn to naturally-occurring allelic variants of a nucleic acid encoding SEQ ID NO: 28, or nucleic acids encoding a naturally-occurring allelic variant of a polypeptide of SEQ ID NO: 28, or nucleic acids which hybridizes to a nucleic acid encoding SEQ ID NO: 28, or nucleic acids which comprises a sequence that differs at no more

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than 20% of the nucleotides in the coding sequence. These are genus claims because the claims are directed to variant nucleic acids encoding variant polypeptides. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, SEQ ID NO: 28 is insufficient to describe the genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information

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regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites the term "stringent conditions", which is a conditional term and renders the claim indefinite. Furthermore, some nucleic acids which might hybridize under conditions of

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moderate stringency, for example, would fail to hybridize under conditions of high stringency.

The metes and bounds of the claim thus cannot be ascertained. This rejection could be obviated by supplying specific conditions supported by the specification which Applicant considers to be "stringent". Claims 13-14 are rejected insofar as they depend on the recitation in claim 12 of "stringent conditions".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10, 12-14 rejected under 35 U.S.C. 102(b) as being anticipated by Ritter et al.

(1990)

The claims are drawn to nucleic acids which hybridize to SEQ ID NO: 27, vectors comprising these nucleic acids, and host cells comprising the vector. The Ritter et al. reference teaches the cloning and expression of the human cDNA clone, UDPGTh-2, encoding a liver UDP-glucuronosyltransferase (transferase) which was isolated from a lambda gt11 cDNA library by hybridization to the mouse transferase cDNA clone, UDPGTm-1. The nucleic acid encoding the UDP-glucuronosyltransferase is 60.6% identical to the nucleic acid of SEQ ID NO: 27 (see

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Sequence Comparison A, attached), and would hybridize under stringent conditions to the nucleic acid. The nucleic acid encoding the UDP-glucuronosyltransferase was cloned into a vector and expressed in host cells (see page 7901, column 1, third full paragraph), thus claims 12-14 are anticipated.

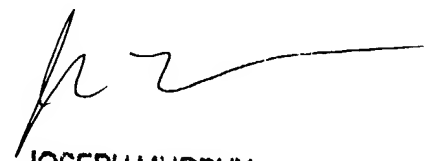
Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
August 2, 2004



JOSEPH MURPHY
PATENT EXAMINER

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RESULT 6
HUMUDPGTA
LOCUS          HUMUDPGTA          1855 bp      mRNA      linear      PRI 03-AUG-1993
DEFINITION     Human 3,4-catechol estrogen UDP-glucuronosyltransferase mRNA,
                complete cds.
ACCESSION      J05428
VERSION        J05428.1  GI:340079
KEYWORDS       3,4-catechol estrogen UDP-glucuronosyltransferase.
SOURCE         Homo sapiens (human)
ORGANISM       Homo sapiens
                Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
                Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE      1 (bases 1 to 1855)
AUTHORS        Ritter,J.K., Sheen,Y.Y. and Owens,I.S.
TITLE          Cloning and expression of human liver UDP-glucuronosyltransferase
                in COS-1 cells. 3,4-catechol estrogens and estriol as primary
                substrates
JOURNAL        J. Biol. Chem. 265 (14), 7900-7906 (1990)
MEDLINE        90243659
PUBMED         2159463
COMMENT        Original source text: Human liver, cDNA to mRNA, clone 63-11.
                Draft entry and computer-readable sequence for [1] kindly submitted
                by I.S.Owens, 22-FEB-1990.
FEATURES
    source      Location/Qualifiers
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                /db_xref="taxon:9606"
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                DTFWLYFSQVQEIMSI FGDI TRKFCKD VVS NKKFMKKVQESRFDVIFADAIFPCSELL
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ORIGIN
Query Match          60.6%;  Score 973;  DB 9;  Length 1855;
Best Local Similarity 78.3%;  Pred. No. 1e-212;
Matches 1265;  Conservative 0;  Mismatches 320;  Indels 30;  Gaps 7;

Qy      1  ATGGCTATGAAATGGACTTCAGTCTCTTCTGTTGATACAGCTGAGCTATTACTCTAGCTCT  60
      ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
Db      15  ATGTCTGTGAAATGGACTTCAGTAATTTTGCTAATACAACCTGAGCTTTTGCTTTAGCTCT  74

Qy      61  GGGAGTGTGGAAATGTGCCGCTGTGGCCCATGGAATATAGTCCTTGGATGAATATAAAG  120
      ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
Db      75  GGGAATGTGGAAAGGTGCTGGTGTGGGCAGCAGAATACAGCCATTGGATGAATATAAAG  134

Qy      121  ACAATCCTGGATAAACTTATGCAGATAAGTCATGAGGTGACTGTTCTAACATTGTCAGCT  180
      ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
Db      135  ACAATCCTGGATGAGCTTATTTCAGAGAGGTGTCATGAGGTGACTGTACTGGCATCTTCAGCT  194

Qy      181  TCCATTCTTGTGTATCCCAACATAACATCTGTTACTAAATTTGAGGTTTATTCTATATCT  240
      ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| ||| |||
Db      195  TCCATTCTTTTGTATCCCAACAACTCATCCGCTCTTAAATTTGAAATTTATCCACATCT  254

Qy      241  GTAATTAAGATGATTTTGCAGGGTTTTTTTTTCACACAACAGATTACTAAATGGATACAT  300

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Db	255	TTAACTAAACTGAGTT---GGAGAATTTTCATCATGCAACAGATTAAAGAGATGGTCA---	308
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Db	309	GACCTTCCAAAAGATACATTTTGGTTATATTTTCACAAGTACAGGAAATCATGTCAATA	368
Qy	361	TATTCTGGTTATACTGAGAAGTTCTTTAAAGATGTAGTTTGAACAAGAAACTTATGACA	420
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Qy	421	AACCTACAAGAATCAAGGTCTGATGTCGTTTCATGCAAATGCCATTGGTCCCTTTGGAGAG	480
Db	429	AAAGTACAAGAGTCAAGATTTGACGTCATTTTGCAGATGCTATTTTCCCTGTAGTGAG	488
Qy	481	CTGCTGGCTGAGCTATTAAAAATATCCTTTGTGTACAGTCTCCACTTCTCTCCTGGCTAC	540
Db	489	CTGCTGGCTGAGCTATTAAACATACCCTTTGTGTACAGTCTCAGCTTCTCTCCTGGCTAC	548
Qy	541	ACATTTGAGAAATACAGTGGAGGATTCTACTTCCACCTTCTATGGAGCTGTTATTCTG	600
Db	549	ACTTTTGAAAAGCATAGTGGAGGATTATTTTCCCTCCTTCTACGTACCTGTTGTTATG	608
Qy	601	TCAGAATTAAGTGGTTCGATGACATTCATGGAGACAGTAAGAAATATTATATATGTGTTT	660
Db	609	TCAGAATTAAGTGCATCAATGACTTTCATGGAGAGGGTAAAAATATGATCTATGTGCTT	668
Qy	661	TATTTTGACTTTTGGTTCCAAACATTGATATGAAGAAGGGAGACCAGTTTACAGTGAA	720
Db	669	TACTTTGACTTTTGGTTCGAAATATTGACATGAAGAAGTGGGATCAGTTTATAGTGAA	728
Qy	721	GTTCTAGGTAAGTCATGTTTTTTATCTGAGATAATGGGAAAAGCTGAAATGTGGCTCATT	780
Db	729	GTTCTAGGAAGACCCACTACGTTATCTGAGACAATGGGAAAAGCTGACGTATGGCTTATT	788
Qy	781	CGAAACTACTGGTATTTGGAATTTCTCGCCCACTCTTACCTAATTTGAATTTGTTGTA	840
Db	789	CGAAACTCCTGGAATTTTCAGTTTCTCATCCACTCTTACCAAATGTTGATTTTGTGGA	848
Qy	841	AGACTCTACTGCAAACCTGTCAACCCCTGCCTAAGGAGAAAATGGAAGAATTTGCCAG	900
Db	849	GGACTCCACTGCAAACCTGCCAAACCCCTGCCTAAGG---AAATGGAAGACTTTGTACAG	905
Qy	901	AGCTCTGATGAAGACGGTGT---GTGTTTTCTCTGGAGTCAGCTGTGCAAAACCTTACA	957
Db	906	AGCTCTGGAGAAAATGGTGTGTGGTGTCTCTCTGGGGTCAATGGTCAGTAACATGACA	965
Qy	958	GAAGAAAAGCTGATCTTATCACTTCGGCCCTGGCTCAGATTCCACAAAAGTCATGAAG	1017
Db	966	GAAGAAAGGGCCAACGTAATTGCATCAGCCCTGGCCAGATCCACAAAAGGTTCTGTGG	1025
Qy	1018	-----TTCGGAAGGAAACCAAATACCTTAAGATCCAATACTCAGTGGCATAGGTGGATC	1071
Db	1026	AGATTTGATGGGAATAAACCCAGATACCTTAGGTCTCAATACTCGGCTGTATAAGTGGATA	1085
Qy	1072	CCACAGAATGAATGTCTTATCCTAGATCATCCCCAAACCAAAGCCTTTATAACTTATGGT	1131
Db	1086	CCCCAGAATGA-----CCTTCTAGGTCATCCAAGACCAGAGCTTTTATAACTCATGGT	1139
Qy	1132	GGAACAAATAGCATCTATGAGATGATCTACCGTGGAGTCCCTTCCATGGGCATTCCCTTG	1191
Db	1140	GGAGCCAATGGCATCTACGAGGCAATCTACCATGGGATCCCTATGGTGGGGATTCCATTG	1199
Qy	1192	TTTGGCGACCAACATGATAACATTGCTCACATGAAGGCCAAGGGAGCAGCTGTTATATTG	1251
Db	1200	TTTGCCGATCAACCTGATAACATTGCTCACATGAAGGCCAGGGGAGCAGCTGTTAGAGTG	1259
Qy	1252	GACTTGAGCACAAAGTCAAGTACAGATTGCTCGATATATCTGTGTTCTGATCTTTATTT	1311
Db	1260	GACTTCAACACAATGTCGAGTACAGACTTGCTGAATGCATTGAAGAGAGTAATTAATGAT	1319

Qy	1312	TTATCCTTCAGATATAAAGAGAGTGTATGAAATTATCAAGAATTCAACATGATCAACCA	1371
Db	1320	CCTTC-----ATATAAAGAGAATGTTATGAAATTATCAAGAATTCAACATGATCAACCA	1373
Qy	1372	GTGAAGCCCTGGATCGAGCAGTCTTCTGGATTGAATTTGTCATGCGCCACAAAGGAGCC	1431
Db	1374	GTGAAGCCCTGGATCGAGCAGTCTTCTGGATTGAATTTGTCATGCGCCACAAAGGAGCT	1433
Qy	1432	AAACACCTTCGAGTTGCAGCCCGTGACCTCACCTGGTTCAGTACCACTCTTTGGATGTG	1491
Db	1434	AAACACCTTCGGGTTGCAGCCACGACCTCACCTGGTTCAGTACCACTCTTTGGATGTG	1493
Qy	1492	ATTGGGTTTCTGCTGGCCTGTGTGGCAACTGTGACATTTATCATCACAAAGTGTGTCTG	1551
Db	1494	ATTGGGTTTCTGCTGGTCTGTGTGGCAACTGTGATATTTATCGTCACAAATGTTGTCTG	1553
Qy	1552	TTTTGTTTCTGGAAGTTTACTAGAAAAGTGAAGAAGGAAAAAAGGGATTAGTTAT	1606
Db	1554	TTTTGTTTCTGGAAGTTTGCTAGAAAAGCAAAGAAGGAAAAAATGATTAGTTAT	1608